# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 50-785

## ADMINISTRATIVE DOCUMENTS

**CONSULTATION RESPONSE**
**Office of Post-Marketing Drug Risk Assessment**
**(OPDRA; HFD-400)**

| **DATE RECEIVED:** July 31, 2001 | **DUE DATE:** August 24, 2001 | **OPDRA CONSULT #:** 01-0076-1 |
|---|---|---|

**TO:** Janice Soreth, MD
Acting Director, Division of Anti-Infective Drug Products
HFD-520

**THROUGH:** Susmita Samanta, Project Manager
HFD-520

| **PRODUCT NAME:** | **NDA HOLDER:** GlaxoSmithKline |
|---|---|
| **Augmentin XR**<br>(amoxicillin/clavulanate potassium extended-release tablets)<br>1000 mg/62.5 mg<br><br>**NDA #: 50-785** | |

**SAFETY EVALUATOR:** Alina R. Mahmud, RPh.

**SUMMARY:** In response to a consult from the Division of Anti-Infective Drug Products (HFD-520), OPDRA conducted a review to evaluate the appropriateness of the modifier "XR" with the proprietary name "Augmentin" to determine the potential for confusion with approved proprietary names and generic names as well as pending names.

**OPDRA RECOMMENDATION:** OPDRA does not object to the use of the proposed modifier "XR" with the approved proprietary name "Augmentin", if the Division agrees that this is truly an extended-release tablet.

APPEARS THIS WAY
ON ORIGINAL

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

**Office of Post-Marketing Drug Risk Assessment**
**HFD-400; Rm. 15B32**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** **August 17, 2001**

**NDA NUMBER:** **50-785**

**NAME OF DRUG:** **Augmentin XR**
(amoxicillin/clavulanate potassium extended-release tablets)
1000 mg/62.5 mg

**NDA HOLDER:** **GlaxoSmithKline**

## I. INTRODUCTION

This consult was written in response to a secondary request from the Division of Anti-Infective Drug Products (HFD-520) regarding the proposed modifier "XR" with the approved proprietary name "Augmentin" to determine the potential for confusion with approved proprietary names and generic names as well as pending names.

OPDRA initially reviewed the proprietary name "Augmentin ES" on May 17, 2000 for the 600 mg/5 mL (600 mg of amoxicillin and 42.9 mg of clavulanate potassium) application under NDA 50-755. The ratio of amoxicillin to clavulanate potassium is 14:1. OPDRA did not recommend the modifier "ES" to the Augmentin name for the new strength. The modifier "ES" implies extra strength and this could be misleading, since Augmentin 875 tablet is currently available. OPDRA recommended the proprietary name Augmentin 600, which is consistent with the existing nomenclature and naming for the oral solutions (Augmentin 125, Augmentin 200, Augmentin 250, and Augmentin 400).

Following a July 19, 2000 meeting with the sponsor, the division decided to accept the name Augmentin ES since there was no safety issue. In addition, the sponsor reported that —

On December 20, 2000 the Sponsor submitted NDA 50-785 for a higher strength of Augmentin extended-release tablets which contain 1000 mg of amoxicillin and 62.5 mg of clavulanate potassium. The ratio of amoxicillin to clavulanate potassium is 16:1. The sponsor requested the use of the proprietary name "Augmentin —" for this new strength —

However, on June 18, 2001 the sponsor withdrew the Augmentin [redacted] name from the tablet product. [redacted]

## II. SAFETY EVALUATOR RISK ASSESSMENT

"XR" is a common modifier used to express an extended-release formuation. There are many approved extended-release drug products with proprietary names that contain the modifier "XR" such as Tegretol XR, Voltaren XR, Dilacor XR, Glucophage XR, and Effexor XR. Therefore, OPDRA has no objections to the use of the modifier "XR" with the approved proprietary name "Augmentin" for the 1000 mg extended-release tablet formulation. This is contingent on the fact that this drug product is truly an extended-release formulation.

## III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the draft container label, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified the following areas of possible improvement, in the interest of minimizing potential user error.

- *Container Label* [redacted]

1. When reviewing a comparison of the various Augmentin labels, we observe that the expression of strength (1000 mg) is less prominent. We would recommend increasing the prominence to be similar to the other strengths.

2. We see no reason to state that [redacted] We find this quite distracting and recommend it be deleted. This would be consistent with the 20 tablet package sizes of 500 mg and 875 mg (both 10 day course of treatment).

## IV. RECOMMENDATIONS

A. OPDRA has no objections to the use of the modifier "XR" with the approved proprietary name "Augmentin", if the Division agrees that this is truly an extended-release tablet.

B. OPDRA has recommended labeling interventions that might minimize user error.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3231.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
---
Alina Mahmud
8/22/01 11:29:28 AM
PHARMACIST

Jerry Phillips
8/22/01 12:57:25 PM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

## Division of Anti-Infective Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-520
Rockville, MD 20850

### FACSIMILE TRANSMISSION

DATE: 12-13-01 Number of Pages (including cover sheet): 5

TO: Mr. Ed Yuhas

COMPANY: GlaxoSmithKline

FAX NUMBER: 215-751-4926

MESSAGE: Faxing Action letter for NDA 50-785, Augmentin XR

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Susmita Samanta

TITLE: Regulatory Project Manager

TELEPHONE: 301-827-2125 FAX NUMBER: 301-827-2327/2325

WITHHOLD 109 PAGE (S)

Draft Labeling

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

# USER FEE COVER SHEET

***See Instructions on Reverse Side Before Completing This Form***

1. APPLICANT'S NAME AND ADDRESS

SmithKline Beecham Pharmaceuticals
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101-7929

2. TELEPHONE NUMBER *(Include Area Code)*

( 215 ) 751-3468

3. PRODUCT NAME

Augmentin —

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

4064

6. LICENSE NUMBER / NDA NUMBER

N050X785

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

**FOR BIOLOGICAL PRODUCTS ONLY**

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

***A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.***



| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE | TITLE | DATE |
|---|---|---|
| Cynthia K. Feinstein | Associate Director U.S. Regulatory Affairs | 12/11/2000 |

FORM FDA 3397 (5/98)

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SmithKline Beecham

# Augmentin (amoxicillin/clavulanate)

## BRL-025000

### Item 16. Debarment Certification

APPEARS THIS WAY
ON ORIGINAL

SB Document Number: BRL-025000/RSD-101GNT/1

APPEARS THIS WAY
ON ORIGINAL

## Item 16. Debarment Certification

Pursuant to section 306(K)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

APPEARS THIS WAY
ON ORIGINAL

SmithKline Beecham

TO: Deneen Stewart
US Regulatory Affairs

FROM: Dara L. Dinner
Associate Patent Counsel
SB Corporate IP - US

DATE: 6 December 2000

RE: Patent Information Respecting Augmentin – New Drug Application (# 50-758) for Management of Specific Bacterial Infections

Please find below the patent information that SB is required to submit to the U.S. FDA under the provisions of 21 C.F.R. § 314.53 for the "Description" and "How Supplied" sections of the labeling.*

The composition for which approval is being sought is a formulation having an approximate ratio of 16:1 of amoxicillin and potassium clavulanate in a bilayer tablet dosage form. The immediate release layer of the bilayer tablet contains approximately [redacted]; and in the sustained release layer there is approximately [redacted]. Thus, each tablet provides a total of 1000 mg amoxicillin and 62.5 mg clavulanic acid (16:1 ratio).

APPEARS THIS WAY
ON ORIGINAL

*Patent Information for NDA Filings (7 Patents)*

**Patent 1: U.S. Patent No. 6,031,093[1]**

a. Expiration Date

The 17 year term expires on 28 February 2017.

b. Type of Patent

This patent claims:

1) a solid pharmaceutically acceptable salt of clavulanic acid which is a component of the formulation for which approval is being sought.

c. Name of Patent Owner

SmithKline Beecham p.l.c.

***Patent 2: U.S. Patent Number 6,048,977***

a. Expiration Date

The 17 year term expires on 28 February 2017.

b. Type of Patent

This patent claims:

1) potassium salt of clavulanic acid which is a component of the formulation for which approval is being sought.

c. Name of Patent Owner

SmithKline Beecham p.l.c.

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[1] FDA recently issued a proposed rule entitled "Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs" (65 Fed. Reg. 3623, Jan. 24, 2000) which the agency attempted to bring its regulations into conformance with certain transitional provisions of the Food and Drug Administration Modernization Act (Section 125 (d) of FDAMA (1997)). In this proposed rule, FDA would exempt marketing applications for certain antibiotic drug products from regulatory provisions governing exclusivity and patents based on a comparison of active moieties. SB disagrees with this proposed rule because it does not reflect Congress's intent for repealing Section 507 of the FD&C Act. SB intends to provide comments to the docket expressing our disagreement with this proposed rule and believes the rule should be changed to reflect these comments. SB was required to perform clinical studies on *Augmentin* ™ to show that it is safe and effective for its intended use. Therefore, the product should receive three years exclusivity under the Hatch-Waxman Act, which is the same period that is available to non-antibiotic drugs

***Patent 3: U.S. Patent Number 6,051,703***

a. Expiration Date

The 17 year term expires on 28 February 2017.

b. Type of Patent

This patent claims:

1) a purified pharmaceutically acceptable salt of clavulanic acid which is a component of the formulation for which approval is being sought.

2) a purified solid pharmaceutically acceptable salt of clavulanic acid which is a component of the formulation for which approval is being sought.

3) purified clavulanic acid or a pharmaceutically acceptable salt thereof, which is a component of the formulation for which approval is being sought.

c. Name of Patent Owner

SmithKline Beecham p.l.c.

***Patent 4: U.S. Patent Number 4,529,720***

a. Expiration Date

The 17 year term expires on July 16, 2002.

b. Type of Patent

This patent claims:

1) generically, a method of effecting β-lactamase inhibition in a human [with β-lactamase producing bacteria] with clavulanic acid or a pharmaceutically acceptable salt thereof, which claims contain a component of the formulation for which approval is being sought.

2) specifically claims the administration of the potassium salt of clavulanic acid, and also oral administration of clavulanic acid or salt thereof,

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and purely synthetic antibiotic drugs. For this reason, we are submitting the patent information on *Augmentin* ~ to receive three years exclusivity and to be listed in The Orange Book.

which claims cover a component of the formulation for which approval is being sought.

c. Name of Patent Owner

Beecham Group, p.l.c.

***Patent 5: U.S. Patent Number 4,560,552***

a. Expiration Date

The 17 year term expires on December 24, 2002

b. Type of Patent

This patent claims:

1) a generic pharmaceutical composition for treating bacterial infections in a human with a synergistically effective amount of clavulanic acid, or a pharmaceutically acceptable salt thereof, and an antibacterially effective amount of a penicillin, or a pharmaceutically acceptable salt or ester thereof, which claims cover the both active ingredients in the formulation for which approval is being sought.

c. Name of Patent Owner

Beecham Group p.l.c.

***Patent 6: U.S. Patent Number 4,525,352***

a. Expiration Date

The 17 year term expires on June 25, 2002

b. Type of Patent

This patent claims:

1) a generic pharmaceutical composition for treating bacterial infections in a human with a synergistically effective amount of a pharmaceutically acceptable salt of clavulanic acid, and an antibacterially effective amount of amoxicillin, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof, in combination

with a pharmaceutically acceptable carrier, which claims cover both of the active ingredients in the formulation for which approval is being sought.

2) specifically claims the potassium salt of clavulanic acid, as a component of the formulation for which approval is being sought.

3) specifically claims the trihydrate form of amoxycillin, as a component of the formulation for which approval is being sought.

4) a generic method of treating bacterial infections in humans with a synergistically effective amount of a pharmaceutically acceptable salt of clavulanic acid, and an antibacterially effective amount of amoxicillin, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable ester thereof, in combination with a pharmaceutically acceptable carrier, which claims a use for which approval is being sought.

5) specifically claims the potassium salt of clavulanic acid and amoxicillin trihydrate, which claims cover use of both active agents in the formulation for which approval is being sought.

c. Name of Patent Owner

Beecham Group p.l.c.

***Patent 7: U.S. Patent Number 4,454,069***

a. Expiration Date

The 17 year term expires on June 12, 2001.

b. Type of Patent

This patent claims:

1) a method for the production of clavulanic acid, or a pharmaceutically acceptable salt thereof, which claims cover production of a component of the formulation for which approval is being sought.

c. Name of Patent Owner

Beecham Group Limited

New drug applications under section 505(b) for drugs that contain "old" antibiotics are not eligible for exclusivity under sections 505(c)

**Confidential**

SmithKline Beecham

# Augmentin (amoxicillin/clavulanate)

## BRL-025000

### Item 15. Establishment Description

Sharon Maglennon*

*USRA

SB Document Number: BRL-025000/RSD-101GNX/1

ACTIVE INGREDIENT (AMOXICILLIN TRIHYDRATE)

| STEP | NAME & ADDRESS | CONTACT PERSON | TELEPHONE / FAX NUMBERS | ESTABLISHMENT/CFN NUMBERS | DATE READY FOR PAI |
|---|---|---|---|---|---|
| Manufacturing, Release and Stability Testing | SmithKline Beecham Pharmaceuticals<br>38 Quality Road<br>Jurong Industrial Estate<br>Singapore 2261<br><br>Currently approved under DMF ——— | Sharon Maglennon<br>Assistant Director<br>North American<br>Regulatory Affairs<br>SmithKline Beecham<br>Pharmaceuticals | tel: 610-917-6457<br><br>fax: 610-917-4104 | CFN No. FCN 024 | 12/20/00 |
| Manufacturing Release and Stability Testing | SmithKline Beecham Pharmaceuticals<br>Clarendon Road<br>Worthing<br>West Sussex BN14 8QH<br>United Kingdom<br><br>Currently approved under DMF ——— | Sharon Maglennon<br>Assistant Director<br>North American<br>Regulatory Affairs<br>SmithKline Beecham<br>Pharmaceuticals | tel: 610-917-6457<br><br>fax: 610-917-4104 | CFN No. FCUK 691 | 12/20/00 |

APPEARS THIS WAY
ON ORIGINAL

ACTIVE INGREDIENT (CLAVULANATE POTASSIUM [redacted]

| STEP | NAME & ADDRESS | CONTACT PERSON | TELEPHONE / FAX NUMBERS | ESTABLISHMENT/CFN NUMBER | DATE READY FOR PAI |
|---|---|---|---|---|---|
| Manufacturing, Release and Stability Testing | SmithKline Beecham Pharmaceuticals<br>Shewalton Road<br><br>Irvine KA11 SAP<br><br>Ayrshire, Scotland<br>United Kingdom<br><br>Currently approved under DMF [redacted] | Sharon Maglennon<br>Assistant Director<br>Regulatory Affairs – North America<br>SmithKline Beecham Pharmaceuticals | tel: 610-917-6457<br><br>fax: 610-917-4104 | CFN No. FCUK 684 | 12/20/00 |
| Manufacturing, Release and Stability Testing | SmithKline Beecham Pharmaceuticals<br>Clarendon Road<br>Worthing<br>West Sussex BN14 8QH<br>United Kingdom<br><br>Currently approved under DMF [redacted] | Sharon Maglennon<br>Assistant Director<br>Regulatory Affairs – North America<br>SmithKline Beecham Pharmaceuticals | tel: 610-917-6457<br><br>fax: 610-917-4104 | CFN No. FCUK 691 | 12/20/00 |

APPEARS THIS WAY
ON ORIGINAL

ACTIVE INGREDIENT (AMOXICILLIN SODIUM)

| STEP | NAME & ADDRESS | CONTACT PERSON | TELEPHONE / FAX NUMBERS | ESTABLISHMENT/CFN NUMBER | DATE READY FOR PAI |
|---|---|---|---|---|---|
| Manufacturing, Release and Stability Testing | SmithKline Beecham Pharmaceuticals<br>101 Possumtown Road<br>Piscataway, NJ 08854<br><br>Detailed in this NDA 50-785 | Linda Schipmann<br>Quality Assurance Manager<br>and<br>Sharon Maglennon<br>Assistant Director<br>Regulatory Affairs – North America<br>SmithKline Beecham Pharmaceuticals | tel: 732-469-5200<br>ext. 4309<br><br>fax: 732-302-4606<br><br>tel: 610-917-6457<br>fax: 610-917-4104 | Establishment No. 2218963 | 12/20/00 |
| Manufacturing Release and Stability Testing | SmithKline Beecham Pharmaceuticals<br>Clarendon Road<br>Worthing<br>West Sussex BN14 8QH<br>United Kingdom<br><br>Detailed in this NDA 50-785 | Sharon Maglennon<br>Assistant Director<br>Regulatory Affairs – North America<br>SmithKline Beecham Pharmaceuticals | tel: 610-917-6457<br><br>fax: 610-917-4104 | CFN No. FCUK 691 | 12/20/00 |

DRUG PRODUCT / AUGMENTIN —

| STEP | NAME & ADDRESS | CONTACT PERSON | TELEPHONE / FAX NUMBERS | ESTABLISHMENT/CFN NUMBER | DATE READY FOR PAI |
|---|---|---|---|---|---|
| Manufacturing, Packaging, Labeling, Release and Stability Testing | SmithKline Beecham Pharmaceuticals<br>201 Industrial Drive<br>Bristol, TN 37620<br><br>Detailed in this NDA 50-785 | Sharon Maglennon<br>Assistant Director<br>Regulatory Affairs – North America<br>SmithKline Beecham Pharmaceuticals | tel: 610-917-6457<br><br>fax: 610-917-4104 | Establishment No. 1047293 | 12/20/00 |
| [redacted] | [redacted]<br><br>Detailed in this NDA 50-785 | [redacted], Quality Assurance Officer<br><br>and<br>Sharon Maglennon<br>Assistant Director<br>Regulatory Affairs – North America<br>SmithKline Beecham Pharmaceuticals | tel: [redacted]<br>fax: [redacted]<br><br>tel: 610-917-6457<br>fax: 610-917-4104 | Establishment No. [redacted] | 12/20/00 |
| [redacted] | [redacted]<br><br>Detailed in this NDA 50-785 | [redacted]<br>V.P. Regulatory Affairs<br>and<br>Sharon Maglennon<br>Assistant Director<br>Regulatory Affairs – North America<br>SmithKline Beecham Pharmaceuticals | tel: [redacted]<br>fax: [redacted]<br><br>tel: 610-917-6457<br>fax: 610-917-4104 | Establishment No [redacted] | 12/20/00 |

Team Leader Memorandum
NDA 50-785 Augmentin® XR Extended Release Tablets

| | |
|---|---|
| Applicant: | GlaxoSmithKline |
| Product Name: | Augmentin® XR |
| Active Ingredients: | Amoxicillin and Clavulanic Acid |
| Formulation: | Extended release tablets containing 1000 mg of amoxicillin and 62.5 mg of clavulanate |
| Submission Date: | March 29, 2002 |
| Memorandum Date: | September 27, 2002 |

Augmentin® XR is a new formulation of a combination product containing amoxicillin and clavulanate in a 16:1 ratio. Augmentin XR tablets contain 1000 mg of amoxicillin and 62.5 mg of clavulanate. The recommended dose regimen, two tablets every 12 hours for 7-10 days, provides the same daily dose of clavulanate (250 mg/day) as the previously approved 7:1 formulation. However, the daily dose of amoxicillin is more than doubled (4000 mg/day for Augmentin XR compared to 1750 mg/day for the 7:1 tablets). In addition, Augmentin XR has extended release characteristics that maintain higher serum concentrations of amoxicillin over a longer portion of the dosing period.

Augmentin® XR was specifically developed to provide sustained amoxicillin concentrations for treatment of penicillin-resistant *Streptococcus pneumoniae* (PRSP). In pharmacokinetic studies of healthy volunteers, the mean time (expressed as a proportion of the 12-hour dose interval) above a minimum inhibitory concentration (T>MIC) of 4 µg/mL for this product was 49%. There is support in the literature for the concept that T>MIC for amoxicillin correlates with effectiveness against *Streptococcus pneumoniae* in animal models of infection. These results were used by the applicant to support moving into phase 3 trials with this formulation. During review of this application, an important limitation was noted with regard to this pharmacodynamic information. There is a great deal of variability in the serum concentrations of amoxicillin. As a result, roughly 10% (9/55) volunteers had a T>MIC ≤ 32%. Therefore, a proportion of the patient population treated with Augmentin® XR may not achieve adequate T>MIC for Streptococcus pneumoniae with an MIC of 4 µg/mL. This leads to the concern that a proportion of infections due to PRSP with an MIC ≥ 4 µg/mL would not be adequately treated with Augmentin® XR.

Several phase 3 trials of patients with community-acquired pneumonia (CAP) and acute bacterial sinusitis (ABS) were conducted by the applicant. These studies included both blinded, comparator-controlled studies and open-label non-comparative trials. The latter were large studies performed to accumulate clinical data on the use of Augmentin® XR for the treatment of PRSP infections.

In CAP, a controlled study (#546) compared Augmentin® XR with the Augmentin® (7:1) formulation already marketed in the U.S. In this study, clinical success rates at the test of cure visit for the per protocol population were 86.3% for Augmentin® XR and 91.2% for

the Augmentin® 7:1 formulation with a 95% confidence interval for the treatment difference of (-11.0, 1.2). In the intent-to-treat (ITT) population, these rates were 78.0% for Augmentin® XR and 82.6% for the Augmentin® 7:1 formulation with a 95% confidence interval for the treatment difference of (-11.4, 2.3). Similar results were reported in a comparative study (#556) that used a European formulation of Augmentin® (not FDA approved).

The following table summarizes the clinical outcomes in the CAP patients with PRSP treated with Augmentin® XR. When categorized by penicillin MIC, the limited experience in CAP patients with *S. pneumoniae* with a penicillin MIC of 4 µg/mL is apparent. The experience for CAP patients with *S. pneumoniae* isolates with a penicillin MIC of 2 µg/mL is greater. The cure rate and 95% confidence interval are similar to those for penicillin-susceptible *S. pneumoniae*.

| **Clinical Outcome for CAP due to *S. pneumoniae*** | | | | | | |
|---|---|---|---|---|---|---|
| **Penicillin MIC of *S. pneumoniae* Isolates** | **Intent To Treat** | | | **Clinically Evaluable** | | |
| | ***n*/N** | **%** | **95% CI** | ***n*/N** | **%** | **95% CI** |
| All *S. pneumoniae* | 184/214 | 86.0 | -- | 157/172 | 91.3 | -- |
| MIC ≥2.0 µg/ml | 17/20 | 85.0 | 62.1, 96.8 | 14/15 | 93.3 | 68.1, 99.8 |
| MIC = 2.0 µg/ml | 13/14 | 92.9 | 66.1, 99.8 | 10/10 | 100 | 69.2, 100 |
| MIC = 4.0 µg/ml | 4/6 | 66.7 | 22.3, 95.7 | 4/5 | 80.0 | 28.4, 99.5 |

Overall, these results provide substantial evidence for the effectiveness of Augmentin® XR in the treatment of CAP. The experience with PRSP isolates support the activity of Augmentin® XR for the treatment of CAP patients with PRSP isolates that have a penicillin MIC of 2 µg/mL. It should be noted that the controlled studies did not demonstrate a particular advantage to the use of Augmentin® XR over approved formulations of Augmentin®. For patients that do not have PRSP, the Augmentin® 7:1 formulation provides similar effectiveness with less drug. Augmentin XR should be reserved for the treatment CAP patients at risk for PRSP.

For ABS, a controlled study (#550) compared Augmentin® XR with levofloxacin 500 mg/day. In this study, clinical success rates at the test of cure visit for the per protocol population were 83.7% for Augmentin® XR and 84.3% for levofloxacin with a 95% confidence interval of (-9.4, 8.3). In the ITT population, these rates were 76.4% for Augmentin® XR and 83.0% for levofloxacin with a 95% confidence interval for the treatment difference of (-14.9, 1.7).

The table on the following page summarizes the outcomes for ABS patients with PRSP. As with the CAP experience, there is greater experience in ABS patients with *S. pneumoniae* isolates with a penicillin MIC of 2 µg/mL. The point estimate of the cure rate and the 95% confidence interval for these patients are similar to the results for penicillin-susceptible *S. pneumoniae*. The experience with treatment of CAP due to PRSP with a penicillin MIC of 2 µg/mL also lends support to its activity in ABS. Again, there is limited experience with S. pneumoniae isolates with a penicillin MIC of 4 µg/mL.

| Clinical Outcome for ABS | | | | | | |
|---|---|---|---|---|---|---|
| **Penicillin MIC of *S. pneumoniae* Isolates** | **Intent To Treat** | | | **Clinically Evaluable** | | |
| | ***n*/N** | **%** | **95% CI** | ***n*/N** | **%** | **95% CI** |
| All *S. pneumoniae* | 222/240 | 92.5 | – | 210/215 | 97.7 | – |
| MIC ≥2.0 µg/ml | 25/26 | 96.2 | 80.4, 99.9 | 22/23 | 95.7 | 78.1, 99.9 |
| MIC = 2.0 µg/ml | 16/17 | 94.1 | 71.3, 99.9 | 13/14 | 92.9 | 66.1, 99.8 |
| MIC ≥ 4.0 µg/ml | 9/9 | 100 | 66.4, 100 | 9/9 | 100 | 66.4, 100 |

Overall, these results provide substantial evidence for the effectiveness of Augmentin® XR in the treatment of ABS. The experience with PRSP isolates supports the activity of Augmentin® XR for the treatment of ABS patients with PRSP isolates that have a penicillin MIC of 2 µg/mL. For patients with PRSP isolates with higher MIC's, the results look promising, but there are several limitations to the data. There is a higher placebo cure rate for ABS. The 95% confidence interval for ABS patients with PRSP with a penicillin MIC of 4 µg/mL is too wide to conclude that Augmentin® XR is more effective than a placebo. Also, there is inadequate evidence of effectiveness for higher MIC isolates in a more serious disease (i.e., CAP) and there are concerns about the variable pharmacokinetics of Augmentin® XR. At this time, the FDA cannot conclude that substantial evidence of effectiveness for treatment of PRSP isolates with penicillin MIC's of 4 µg/mL or higher for either CAP or ABS. The sponsor has been encouraged to gather more clinical data on treatment of PRSP with penicillin MIC's of 4 µg/mL.

A total of 4144 patients received Augmentin® XR in phase 3 clinical studies. Of these, 2787 patients received Augmentin® XR in non-comparative studies. In comparative trials, 1357 patients received Augmentin® XR and 1387 received comparator drugs. Adverse events (AE) were reported in 52.3% of Augmentin® XR and 51.3% of comparator patients in the comparative trials. The AE rates for Augmentin® XR were lower in the non-comparative trials, so that 1952/4144 (47.1%) of Augmentin® XR patients in phase 3 trials reported AE. The most common AE in Augmentin® XR patients were diarrhea (17.4%), headache (3.8%), nausea (3.3%), abdominal pain (2.5%), and genital moniliasis (2.2%). Overall, the types of AE for Augmentin® XR are similar to those described for FDA approved formulations of Augmentin®. In one CAP trial, there was a direct comparison of Augmentin® XR (255 patients) with the approved Augmentin® 7:1 formulation (259 patients). The overall rates of adverse events were similar (49.4% vs. 51.4%, respectively) in the two treatment arms. The most common AE was diarrhea (18.0% vs. 14.3%, respectively), but the difference was not statistically significant. Still, higher amounts of amoxicillin in Augmentin® XR are expected to result in higher rates of adverse events for any dose-related AE. Diarrhea was reported in 19.8% of Augmentin® XR patients and 9.9% of comparator patients in the comparative trials.

Overall, the applicant has provided substantial evidence of the safety and effectiveness of Augmentin® XR.

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

John Alexander
10/21/02 03:59:59 PM
MEDICAL OFFICER

Team Leader Memo for Augmentin XR resubmission; Please sign off.

Janice Soreth
10/21/02 05:17:45 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

# PEDIATRIC PAGE

## (Complete for all APPROVED original applications and efficacy supplements)

NDA # : 50-785 Supplement Type (e.g. SE5): NA Supplement Number: NA

mp Date: 3/29/02 Action Date: _____

HFD -520 Trade and generic names/dosage form: Augmentin XR™(amoxicillin/clavulanate potassium) 1000/62.5mg Tablet

Applicant: GlaxoSmithKline Therapeutic Class: 3S

Indication(s) previously approved: NA

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 2

Indication #1: Community-Acquired Pneumonia

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

X No: Please check all that apply: X Partial Waiver X Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

## tion A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: _____

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

Age/weight range being partially waived:

| | | | | |
|---|---|---|---|---|
| Min ___ | kg ___ | mo. 0 | yr. ___ | Tanner Stage ___ |
| Max ___ | kg ___ | mo. 3 | yr. ___ | Tanner Stage ___ |

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
X Other: Children between the 0-3 months with this condition are usually treated with IV antibiotics

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.** 3 | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.** 16 | **Tanner Stage**_____ |

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- **X** **Adult studies ready for approval**

**Other:**_____

**Date studies are due (mm/dd/yy):** 09/25/04

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |

**Comments:**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

*{See appended electronic signature page}*

**Regulatory Project Manager**

**cc: NDA**
**HFD-950/ Terrie Crescenzi**
**HFD-960/Grace Carmouze**
**(revised 9-24-02)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960**
**301-594-7337**

## Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** Acute Bacterial Sinusitis

**Is there a full waiver for this indication (check one)?**

- ☐ **Yes: Please proceed to Section A.**

- X **No: Please check all that apply: X Partial Waiver X Deferred ___ Completed**
  **NOTE: More than one may apply**
  **Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

## Section A: Fully Waived Studies

**Reason(s) for full waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

**Age/weight range being partially waived:**

| | | | | | |
|---|---|---|---|---|---|
| **Min** | **kg** | **mo.** 0 | **yr.** | **Tanner Stage** | |
| **Max** | **kg** | **mo.** 3 | **yr.** | **Tanner Stage** | |

**Reason(s) for partial waiver:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- X **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## ion C: Deferred Studies

**Age/weight range being deferred:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.** 3 | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.** 16 | **Tanner Stage**_____ |

**Reason(s) for deferral:**

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- X **Adult studies ready for approval**

☐ **Other:**_____

**Date studies are due (mm/dd/yy): 09/25/02**_____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## ction D: Completed Studies

**Age/weight range of completed studies:**

| | | | | |
|---|---|---|---|---|
| **Min** _____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |
| **Max**_____ | **kg**_____ | **mo.**_____ | **yr.**_____ | **Tanner Stage**_____ |

**Comments:**

***If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.***

**This page was completed by:**

*{See appended electronic signature page}*

_____

**Regulatory Project Manager**

cc: **NDA**
**HFD-960/ Terrie Crescenzi**
**(revised 1-18-02)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960**
**301-594-7337**

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/

John Alexander
10/4/02 01:18:24 PM

APPEARS THIS WAY
ON ORIGINAL